N=1 Human Study in Clinical Neurosciences: Genomics Guided Medicine and Deep Brain Stimulation

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CSH
STANLEY INSTITUTE FOR COGNITIVE GENOMICS
COLD SPRING HARBOR LABORATORY

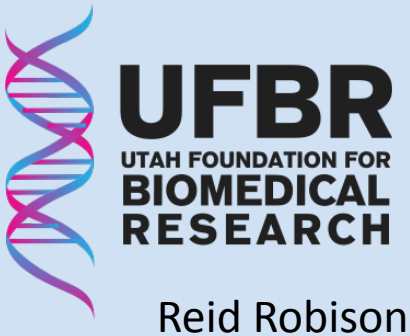
Conflicts of Interest

- I do not receive salary compensation, donations or “gifts” from anyone other than my current employer, CSHL .

- Any revenue that I earn from providing medical care in Utah is donated to UFBR for genetics research.

Acknowledgments

Martin Reese
Edward Kiruluta



Reid Robison

David Mittelman
Gareth Highman

Barry Moore
Alan Rope
Jeffrey J Swensen
Lynn Jorde
Mark Yandell

Jason O'Rawe
Yiyang Wu
Michael Schatz
Giuseppe Narzisi

Kai Wang

Tina Hambuch
Erica Davis
Dawn Barry

our study families

Take Home Message

Genotype ≠ Phenotype

Environment matters!

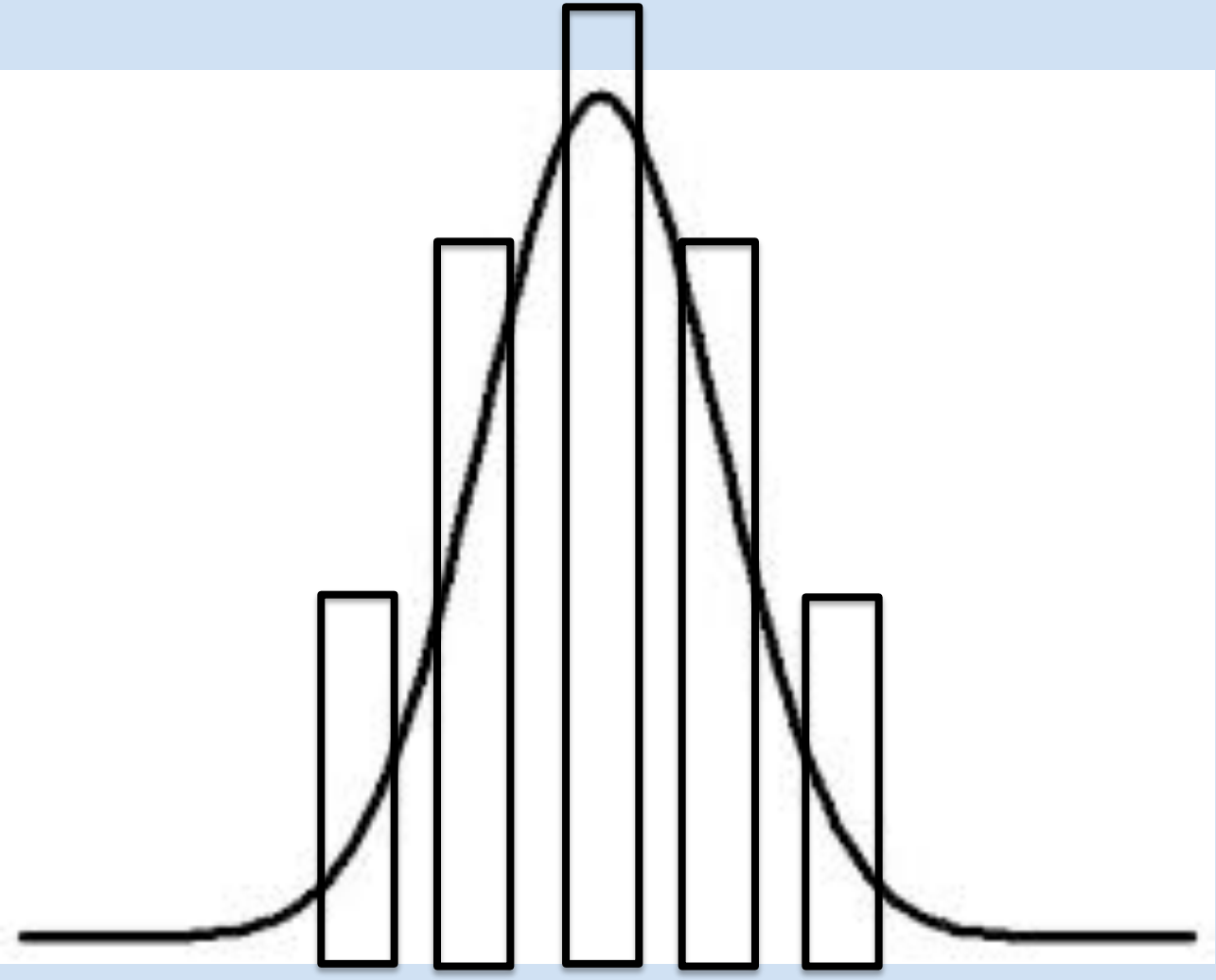
Ancestry matters!

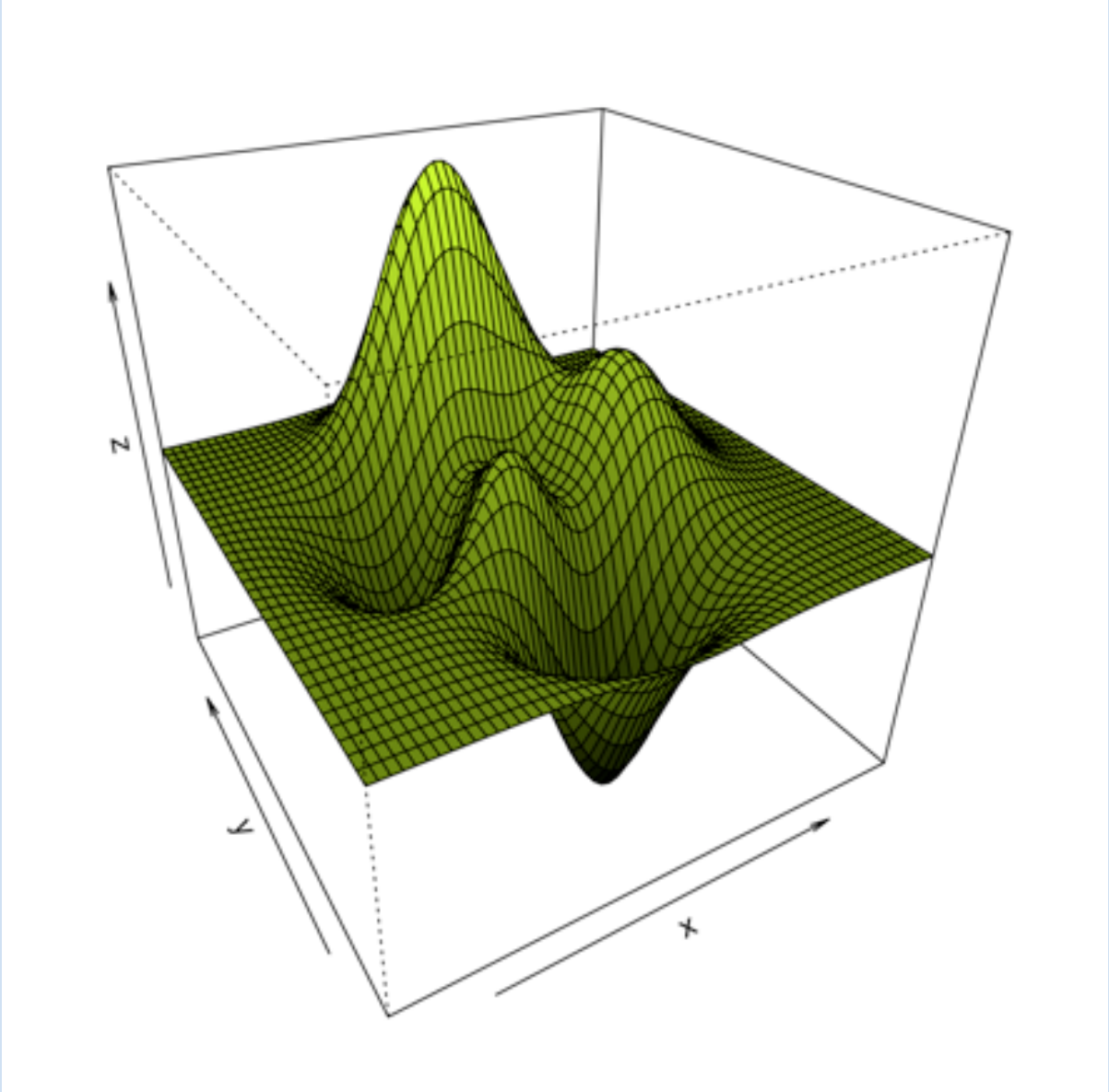
Genomic background matters!

Longitudinal course matters!

We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of consumer owned and managed data.

Categorical Thinking Misses Complexity





A conceptual model of canalization. The *y* plane represents a phenotypic spectrum, the *x* plane represents the canalized progression of development through time, and the *z* plane represents environmental fluctuations.

Expression Issues

- We do not really know the expression of pretty much ALL mutations in **humans**, as we have not systematically sequenced or karyotyped any genetic alteration in **Thousands to Millions** of **randomly** selected people, nor categorized into ethnic classes, i.e. clans.

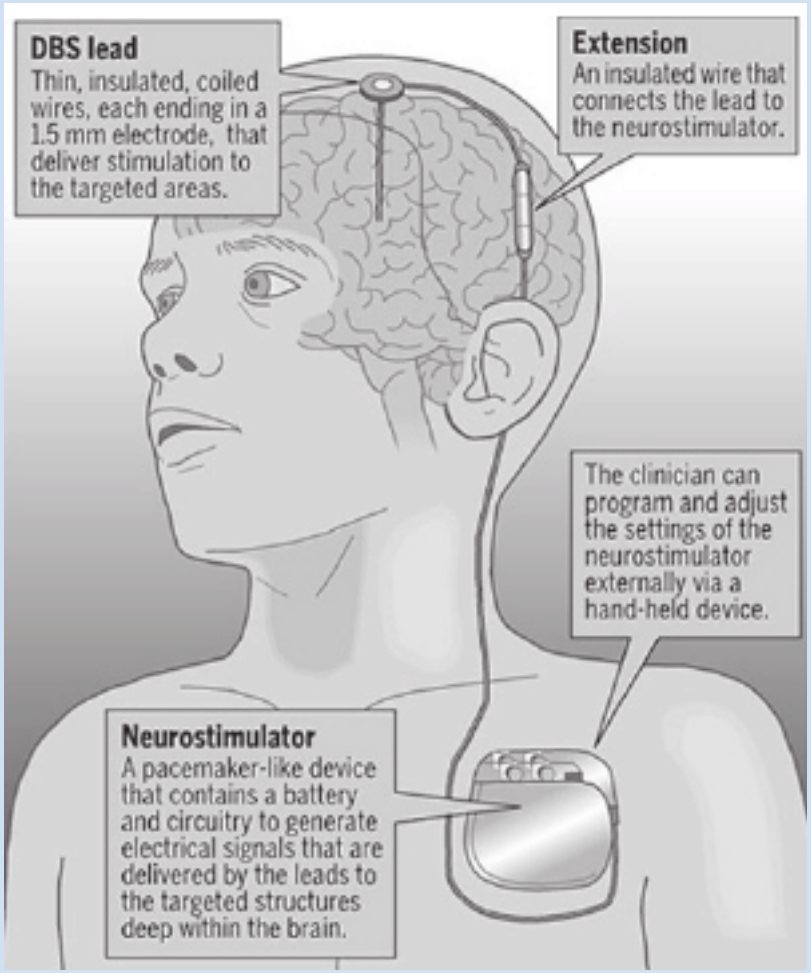
Complexity

- There are ~25-100 TRILLION cells in each human body, with ~6 billion nucleotides per cell.
- There is extensive modification of DNA, RNA and proteins both spatially and temporally.
- There are higher level mechanisms of somatic mosaicism, heterosis, and likely ancestral inheritance.

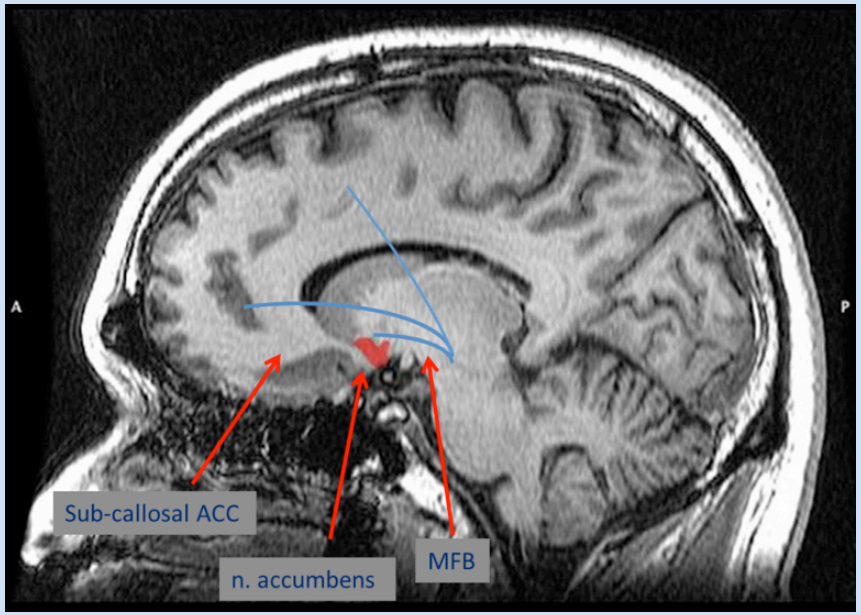
A family in Utah, with a 40 year old Caucasian man with
very severe obsessive compulsive disorder, severe depression and intermittent psychoses, with symptoms that started around age 5.

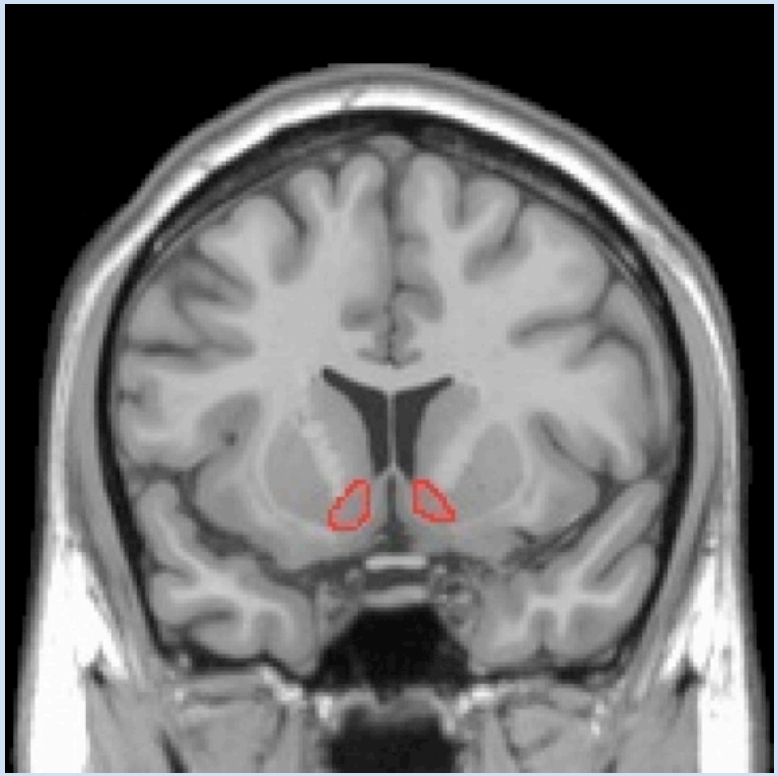
Multiple medication trials failed over many years.
Considered treatment refractory.

Humanitarian Device Exemption (HDE) for OCD



Nucleus accumbens





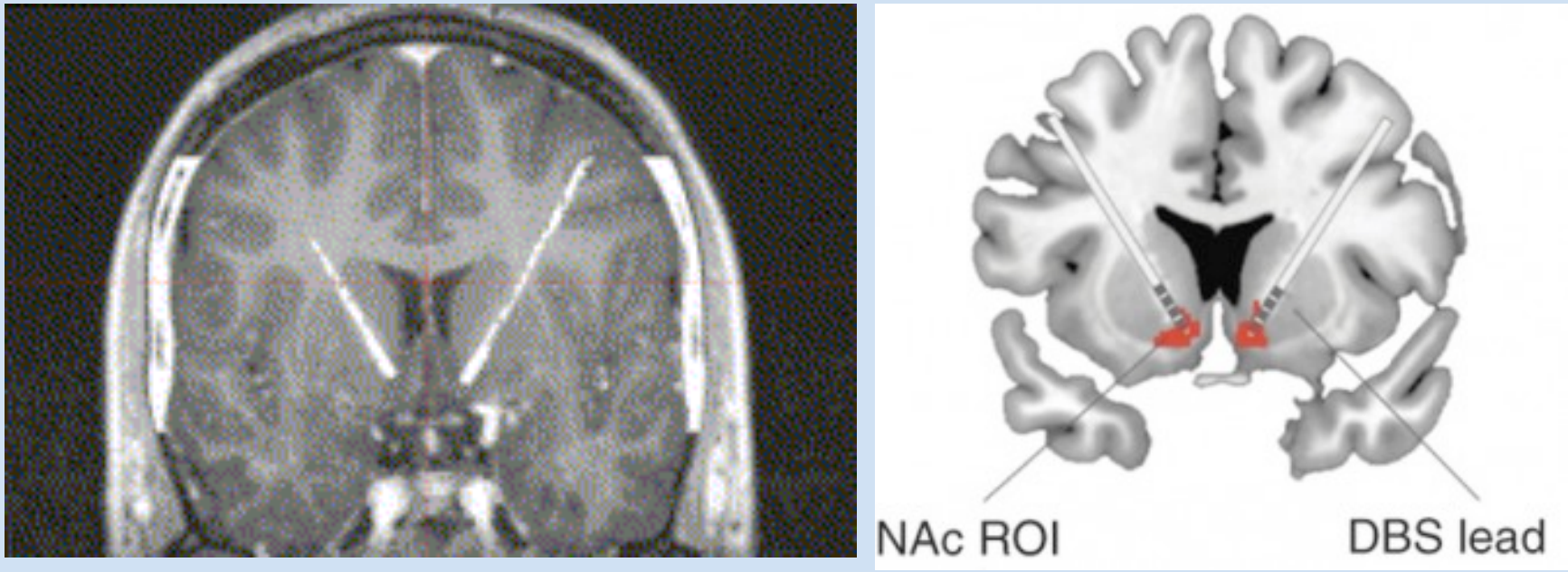
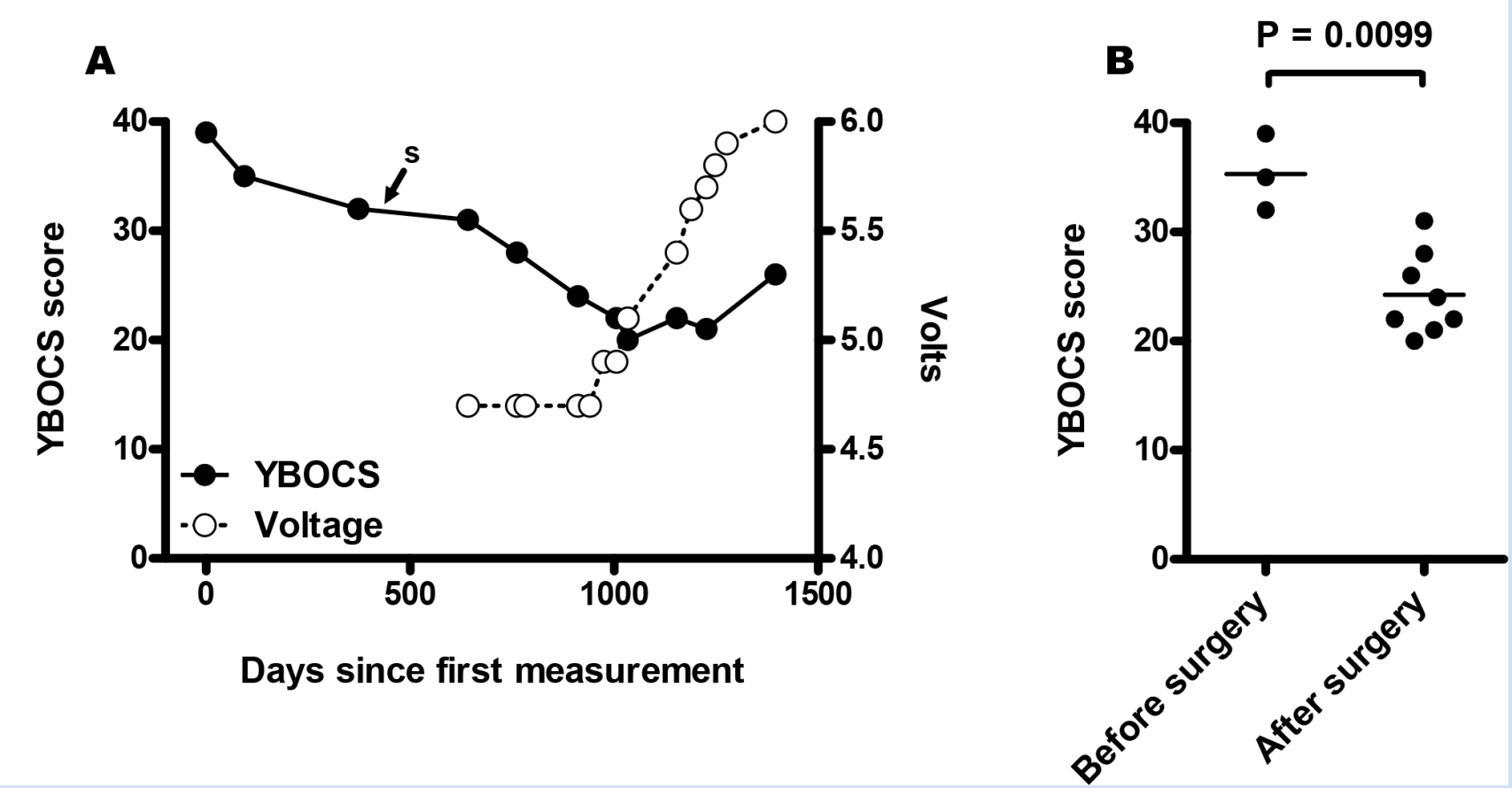


Fig. 1. Coronal section of the brain near the nucleus accumbens with the track of the electrodes on the left and right side.

2.5 year follow-up



Pulse width = 210, Frequency 130 Hz

Global Assessment of Functioning (GAF) 0 to 100 scale

From 5 to 15 in 2008-2009

To

45 to 55 in 2013

Depleteable nature of battery

- Battery replaced with a rechargeable battery in January 2012.
- After the battery was turned off the first time, M.A. was not immediately under any pain. However, after 3 days, M.A. almost attempted suicide because of the increase in depression, anxiety, and physical pain. Even worse, M.A. had little to no insight into his disease, and had an increase in memory and congitive deficit and had thus forgotten the benefits that had been his just a few days prior.
- M.A. decided to kill himself since he was unable to connect the renewal of traumatic symptoms with the battery's termination. Before getting in his car to end his life in another planned car wreck, M.A. saw his battery modulator on the front seat of his car. The modulator could turn his pacemaker on and off. When M.A. saw it, he had a brief moment of clarity about feeling better in the past.
- Unsure if he was delusional or not, M.A. put the device up to his shoulder and turned the battery on. The change was instantaneous.

Contents lists available at SciVerse ScienceDirect

Applied & Translational Genomics

journal homepage: www.elsevier.com/locate/atg

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

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Table 1
Processes involved in a CLIA-certified genetic test.

Preanalytic system
1) Test request and specimen collection criteria
2) Specimen submission, handling and referral procedures
3) Preanalytic systems assessment
Analytic system
1) A detailed step-by-step procedure manual
2) Test systems, equipment, instruments, reagents, materials and supplies
3) Establishment and verification of performance specifications
4) Maintenance and function checks
5) Calibration and calibration verification procedures
6) Control procedures, test records, and corrective actions
7) Analytic systems assessment
Post-analytic system
1) Test report, including (among other things):
a) interpretation
b) reference ranges and normal values
2) Post-analytic systems assessment

1. Sample Collection and handling

2. Sequencing/Analytics

3. Interpretation

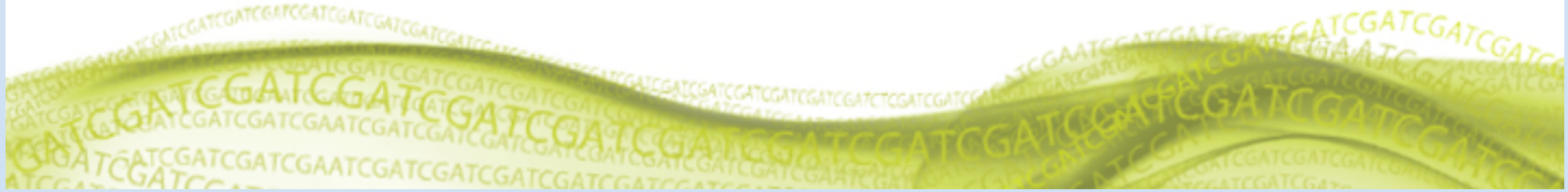
Individual Genome Sequencing Service

Available from Illumina's CLIA-certified laboratory.

"This laboratory test was developed, and its performance characteristics were determined by the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited). Consistent with laboratory-developed tests, it has not been cleared or approved by the U.S. Food and Drug Administration. If you have any questions or concerns about what you might learn through your genome sequence information, you should contact your doctor or a genetic counselor. Please note that Illumina does not accept orders for Individual Genome Sequencing services from Florida and New York."

Understand Your Genome Symposium

During this two-day educational event, industry experts will discuss the clinical implementation of whole-genome next-generation sequencing (NGS) technology.



illumina®

Ordering Physician:
Gholson Lyon, MD
Steinmann Institute
10 West Broadway, Suite #820
Salt Lake City, UT 84101

Individual Genome Sequence Results

Clinical Report

www.everygenome.com
CLIA#: 05D1092911

Sample Collection and Handling

The Sample Collection kit includes barcoded collection tubes, a Test Requisition form, an Informed Patient Consent form, and a pre-paid shipping envelope. All paperwork must be completed and returned for sample processing. Requests for Sample Collection kits must be submitted by a physician.

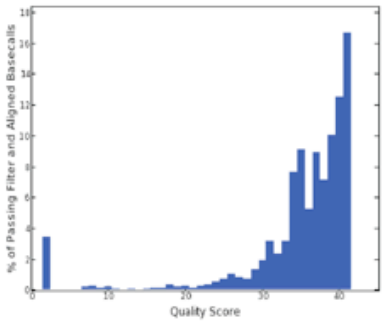
http://www.illumina.com/clinical/illumina_clinical_laboratory/igs_for_doctors/how_to_order.ilmn

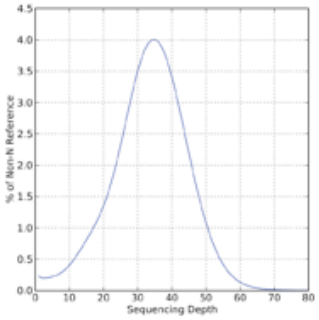
Sequencing and Analytics

Data Volume and Quality

	Yield (Gigabases)	% Bases ≥ Q30	% Bases Aligned
Passing Filter	113.10	87.10%	87.80%

	% Callable	% ≥ 5x depth	% ≥ 10x depth	% ≥ 20x depth	Mean depth(x)
Non-N Reference	93.28%	97.57%	96.22%	88.54%	33.35





SNP Assessment

Total	Het/Hom	% in dbSNP	% in Genes	% in Coding
3,308,246	1.61	98.13%	45.47%	0.63%

Variant Statistics

	SNVs
Total Number	3,308,246
Number in Genes	1,504,121
Number in Coding Regions	20,879
Number in UTRs	24,946
Splice Site Region	2,917
Stop Gained	72
Stop Lost	16
Non-synonymous	9,884
Synonymous	10,907
Mature miRNA	36

From the Illumina Understand Your Genome Symposium October 2012

Evaluation of 344 genes by Illumina

A total of **1247** variants were detected in the subset of genes for this patient. Each variant was evaluated for clinical significance and placed into one of five possible categories for classification, based on the American College of Medical Genetics and Genomics interpretation guidelines as outlined below and described at the end of this report.

Category		Number of Variants	Condition
Clinically Significant in Patient	Pathogenic	0	
	Likely Pathogenic	0	
Carrier Status for Patient	Pathogenic	0	
	Likely Pathogenic	1	Refsum Disease
Variants of Unknown Significance		284	
Likely Benign Variants		349	
Benign Variants		613	

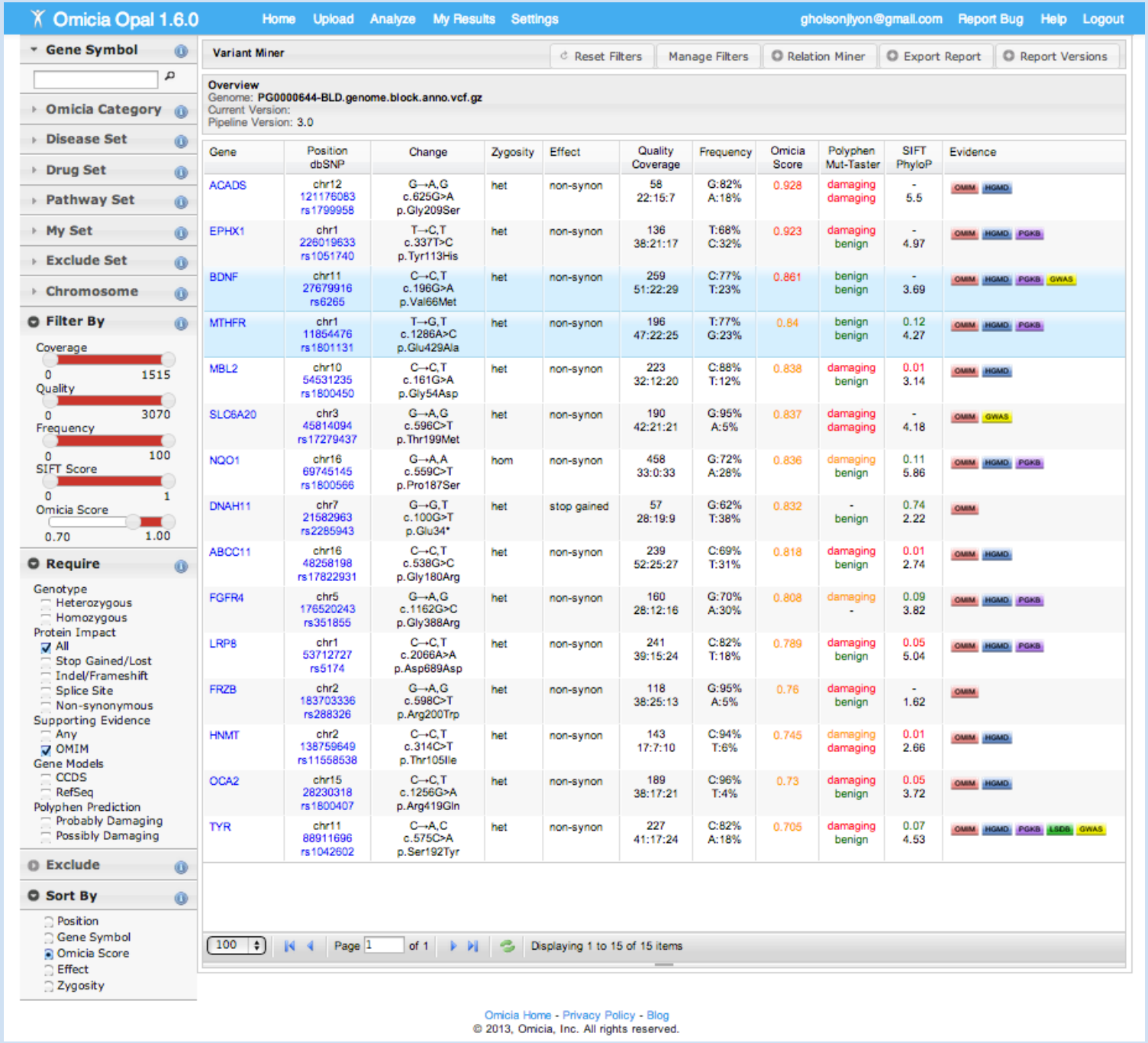
Gene	Call	Amino Acid	Interpretation	Associated Condition	Mode of Inheritance
PHYH	c.734G>A	p.Arg245Gln	Likely Pathogenic	Refsum Disease	Autosomal Recessive

Refsum Disease

Refsum disease is an inherited condition that causes vision loss, anosmia, and a variety of other signs and symptoms. The vision loss is caused by retinitis pigmentosa. The first sign of retinitis pigmentosa is usually a loss of night vision, which often becomes apparent in childhood. Over a period of years, the disease disrupts peripheral vision and may eventually lead to blindness. Vision loss and anosmia are seen in almost everyone with Refsum disease, but other signs and symptoms vary. About one-third of affected individuals are born with bone abnormalities of the hands and feet. Features that appear later in life can include progressive myopathy; ataxia; hearing loss; and ichthyosis. Additionally, some people with Refsum disease develop arrhythmia and cardiomyopathies that can be life-threatening.

Refsum Disease?

- Referred to optometry for further evaluation of this.
- Found to have bilateral cataracts, large pupils, and loss of night vision.
- His mother and grandmother both have large pupils and loss of night vision. No cataracts known.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Omicia Category
Disease Set
Drug Set
Pathway Set
My Set
Exclude Set
Chromosome
Filter By
Coverage
0
1515
Quality
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Frequency
0
100
SIFT Score
0
1
Omicia Score
0.70
1.00
Require
Genotype
Heterozygous
Homozygous
Protein Impact
All
Stop Gained/Lost
Indel/Frameshift
Splice Site
Non-synonymous
Supporting Evidence
Any
OMIM
Gene Models
CCDS
RefSeq
Polyphen Prediction
Probably Damaging
Possibly Damaging
Exclude
Sort By
Position
Gene Symbol
Omicia Score
Effect
Zygosity
Variant Miner
Reset Filters
Manage Filters
Relation Miner
Export Report
Report Versions
Overview
Genome: PG0000644-BLD.genome.block.anno.vcf.gz
Current Version:
Pipeline Version: 3.0
Gene
Position dbSNP
Change
Zygosity
Effect
Quality Coverage
Frequency
Omicia Score
Polyphen Mut-Taster
SIFT PhyloP
Evidence
ACADS chr12 121176083 rs1799958 G→A,G c.625G>A p.Gly209Ser het non-synon 58 22:15:7 G:82% A:18% 0.928 damaging damaging - 5.5 OMIM HGMD
EPHX1 chr1 226019633 rs1051740 T→C,T c.337T>C p.Tyr113His het non-synon 136 38:21:17 T:68% C:32% 0.923 damaging benign - 4.97 OMIM HGMD PGKB
BDNF chr11 27679916 rs6265 C→C,T c.196G>A p.Val66Met het non-synon 259 51:22:29 C:77% T:23% 0.861 benign benign - 3.69 OMIM HGMD PGKB GWAS
MTHFR chr1 11854476 rs1801131 T→G,T c.1286A>C p.Glu429Ala het non-synon 196 47:22:25 T:77% G:23% 0.84 benign benign 0.12 4.27 OMIM HGMD PGKB
MBL2 chr10 54531235 rs1800450 C→C,T c.161G>A p.Gly54Asp het non-synon 223 32:12:20 C:88% T:12% 0.838 damaging benign 0.01 3.14 OMIM HGMD
SLC6A20 chr3 45814094 rs17279437 G→A,G c.596C>T p.Thr199Met het non-synon 190 42:21:21 G:95% A:5% 0.837 damaging damaging - 4.18 OMIM GWAS
NQO1 chr16 69745145 rs1800566 G→A,A c.559C>T p.Pro187Ser hom non-synon 458 33:0:33 G:72% A:28% 0.836 damaging benign 0.11 5.86 OMIM HGMD PGKB
DNAH11 chr7 21582963 rs2285943 G→G,T c.100G>T p.Glu34* het stop gained 57 28:19:9 G:62% T:38% 0.832 - benign 0.74 2.22 OMIM
ABCC11 chr16 48258198 rs17822931 C→C,T c.538G>C p.Gly180Arg het non-synon 239 52:25:27 C:69% T:31% 0.818 damaging benign 0.01 2.74 OMIM HGMD
FGFR4 chr5 176520243 rs351855 G→A,G c.1162G>C p.Gly388Arg het non-synon 160 28:12:16 G:70% A:30% 0.808 damaging - 0.09 3.82 OMIM HGMD PGKB
LRP8 chr1 53712727 rs5174 C→C,T c.2066A>A p.Asp689Asp het non-synon 241 39:15:24 C:82% T:18% 0.789 damaging benign 0.05 5.04 OMIM HGMD PGKB
FRZB chr2 183703336 rs288326 G→A,G c.598C>T p.Arg200Trp het non-synon 118 38:25:13 G:95% A:5% 0.76 damaging benign - 1.62 OMIM
HNMT chr2 138759649 rs11558538 C→C,T c.314C>T p.Thr105Ile het non-synon 143 17:7:10 C:94% T:6% 0.745 damaging damaging 0.01 2.66 OMIM HGMD
OCA2 chr15 28230318 rs1800407 C→C,T c.1256G>A p.Arg419Gln het non-synon 189 38:17:21 C:96% T:4% 0.73 damaging benign 0.05 3.72 OMIM HGMD
TYR chr11 88911696 rs1042602 C→A,C c.575C>A p.Ser192Tyr het non-synon 227 41:17:24 C:82% A:18% 0.705 damaging benign 0.07 4.53 OMIM HGMD PGKB LSDB GWAS
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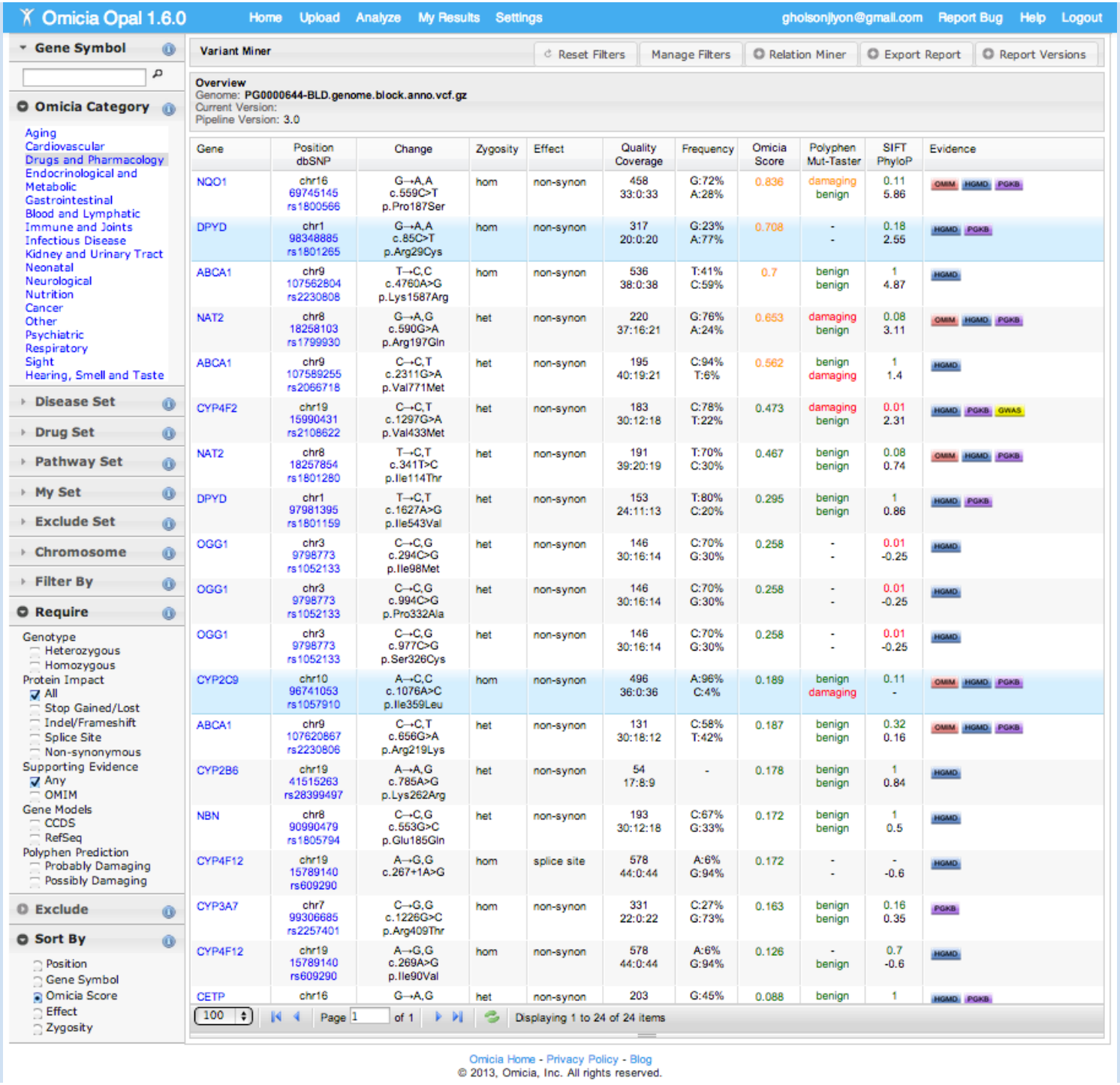
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Gene Symbol
Omicia Category
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Cardiovascular
Drugs and Pharmacology
Endocrinological and Metabolic
Gastrointestinal
Blood and Lymphatic
Immune and Joints
Infectious Disease
Kidney and Urinary Tract
Neonatal
Neurological
Nutrition
Cancer
Other
Psychiatric
Respiratory
Sight
Hearing, Smell and Taste
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Drug Set
Pathway Set
My Set
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Filter By
Require
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Homozygous
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Possibly Damaging
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Zygosity
Variant Miner
Reset Filters
Manage Filters
Relation Miner
Export Report
Report Versions
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Pipeline Version: 3.0
Gene
Position dbSNP
Change
Zygosity
Effect
Quality Coverage
Frequency
Omicia Score
Polyphen Mut-Taster
SIFT PhyloP
Evidence
NQO1 chr16 69745145 rs1800566 G→A,A c.559C>T p.Pro187Ser hom non-synon 458 33:0:33 G:72% A:28% 0.836 damaging benign 0.11 5.86 OMIM HGMD PGKB
DPYD chr1 98348885 rs1801265 G→A,A c.85C>T p.Arg29Cys hom non-synon 317 20:0:20 G:23% A:77% 0.708 - - 0.18 2.55 HGMD PGKB
ABCA1 chr9 107562804 rs2230808 T→C,C c.4760A>G p.Lys1587Arg hom non-synon 536 38:0:38 T:41% C:59% 0.7 benign benign 1 4.87 HGMD
NAT2 chr8 18258103 rs1799930 G→A,G c.590G>A p.Arg197Gln het non-synon 220 37:16:21 G:76% A:24% 0.653 damaging benign 0.08 3.11 OMIM HGMD PGKB
ABCA1 chr9 107589255 rs2066718 C→C,T c.2311G>A p.Val771Met het non-synon 195 40:19:21 C:94% T:6% 0.562 benign damaging 1 1.4 HGMD
CYP4F2 chr19 15990431 rs2108622 C→C,T c.1297G>A p.Val433Met het non-synon 183 30:12:18 C:78% T:22% 0.473 damaging benign 0.01 2.31 HGMD PGKB GWAS
NAT2 chr8 18257854 rs1801280 T→C,T c.341T>C p.Ile114Thr het non-synon 191 39:20:19 T:70% C:30% 0.467 benign benign 0.08 0.74 OMIM HGMD PGKB
DPYD chr1 97981395 rs1801159 T→C,T c.1627A>G p.Ile543Val het non-synon 153 24:11:13 T:80% C:20% 0.295 benign benign 1 0.86 HGMD PGKB
OGG1 chr3 9798773 rs1052133 C→C,G c.294C>G p.Ile98Met het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
OGG1 chr3 9798773 rs1052133 C→C,G c.994C>G p.Pro332Ala het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
OGG1 chr3 9798773 rs1052133 C→C,G c.977C>G p.Ser326Cys het non-synon 146 30:16:14 C:70% G:30% 0.258 - - 0.01 -0.25 HGMD
CYP2C9 chr10 96741053 rs1057910 A→C,C c.1076A>C p.Ile359Leu hom non-synon 496 36:0:36 A:96% C:4% 0.189 benign damaging 0.11 - OMIM HGMD PGKB
ABCA1 chr9 107620867 rs2230806 C→C,T c.656G>A p.Arg219Lys het non-synon 131 30:18:12 C:58% T:42% 0.187 benign benign 0.32 0.16 OMIM HGMD PGKB
CYP2B6 chr19 41515263 rs28399497 A→A,G c.785A>G p.Lys262Arg het non-synon 54 17:8:9 - 0.178 benign benign 1 0.84 HGMD
NBN chr8 90990479 rs1805794 C→C,G c.553G>C p.Glu185Gln het non-synon 193 30:12:18 C:67% G:33% 0.172 benign benign 1 0.5 HGMD
CYP4F12 chr19 15789140 rs609290 A→G,G c.267+1A>G hom splice site 578 44:0:44 A:6% G:94% 0.172 - - - -0.6 HGMD
CYP3A7 chr7 99306685 rs2257401 C→G,G c.1226G>C p.Arg409Thr hom non-synon 331 22:0:22 C:27% G:73% 0.163 benign benign 0.16 0.35 PGKB
CYP4F12 chr19 15789140 rs609290 A→G,G c.269A>G p.Ile90Val hom non-synon 578 44:0:44 A:6% G:94% 0.126 - benign 0.7 -0.6 HGMD
CETP chr16 G→A,G het non-synon 203 G:45% 0.088 benign 1 HGMD PGKB
100
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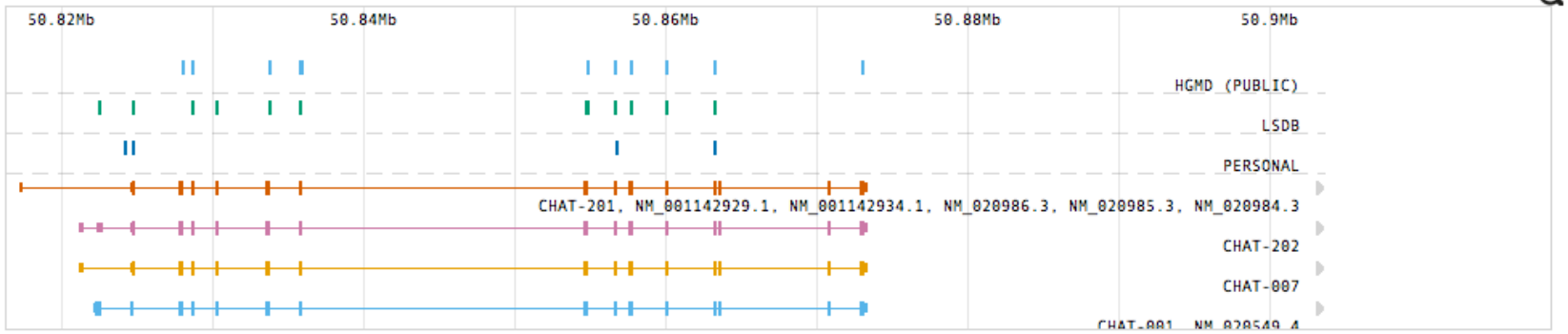
No rare variants or CNVs with high biological effect as related to mental illness.

3 common SNVs in this person that have been implicated in the literature as predisposing to mental illness.

Gene name	Genomic coordinates	Amino acid change	Zygosity	Mutation type	Population Frequency	Clinical significance
MTHFR	chr1: 11854476	Glu>Ala	heterozygous	non-synon	T:77% G:23%	Susceptibility to psychoses, schizophrenia, occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetra-hydrofolate reductase deficiency
BDNF	chr11: 27679916	Val>Met	heterozygous	non-synon	C:77% T:23%	Susceptibility to OCD, psychosis, and diminished response to exposure therapy
CHAT	chr10: 50824117	Asp>Asn	heterozygous	non-synon	G:85% A:15%	Susceptibility to schizophrenia and other psychopathological disorders.

Gene Summary for CHAT



Gene Overview	
Symbol	CHAT
Name	choline O-acetyltransferase
Location	10q11.2
Summary	This gene encodes an enzyme which catalyzes the biosynthesis of the neurotransmitter acetylcholine. This gene product is a characteristic feature of cholinergic neurons, and changes in these neurons may explain some of the symptoms of Alzheimer's disease. Polymorphisms in this gene have been associated with Alzheimer's disease and mild cognitive impairment. Mutations in this gene are associated with congenital myasthenic syndrome associated with episodic apnea. Multiple transcript variants encoding different isoforms have been found for this gene, and some of these variants have been shown to encode more than one isoform. [provided by RefSeq, May 2010]

Relevant Reference Resources	
NCBI Gene	http://www.ncbi.nlm.nih.gov/gene/1103
GeneTests	http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/gene/CHAT
Ensembl	http://www.ensembl.org/human/Gene/Summary?g=ENSG00000070748
UCSC Gene Browser	http://genome.ucsc.edu/cgi-bin/hgTracks?org=human&db=hg19&singleSearch=knownCanonical&position=CHAT
Genetics Home Reference	http://ghr.nlm.nih.gov/gene/CHAT

Associated Disease Categories

Category	Disease	Citation
DRUGS, CLINICAL PHARMACOLOGY AND ENVIRONMENT	Drug toxicity	Roden et al., 2002

Associated Knowledge Sets

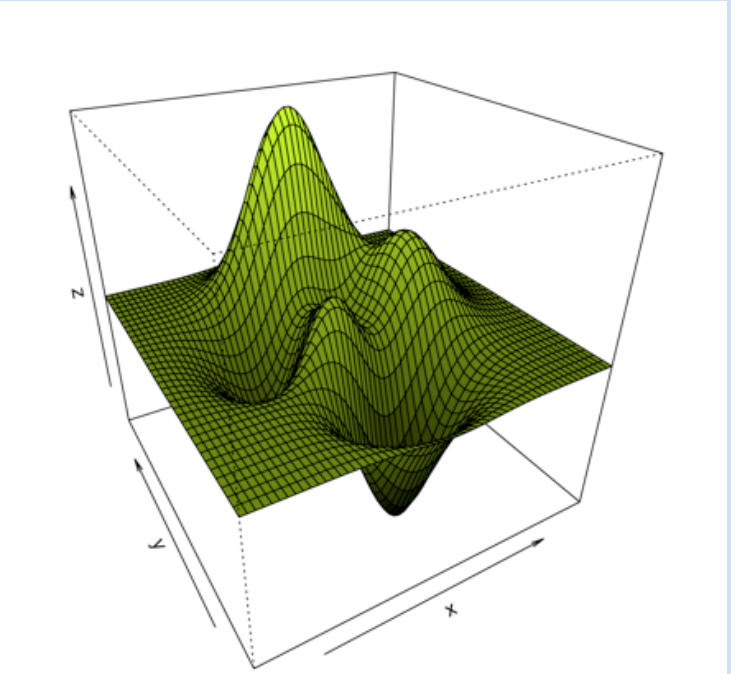
Name	Type	Description
ODG - Alzheimers	disease	Omicia Disease Genes (ODG) Top 10 Neurological - Alzheimers
TruSight Exome	disease	Illumina's targeted rare genetic conditions exome test containing 2,761 genes covered in the HGMD database.
MitoGO	myset	
Longo - Phenomizer Fatty Acid Big	myset	A list of genes from phenomizer build from Patient Features HP:0004359. Long List ~3000 genes

Personal Variants in this Gene

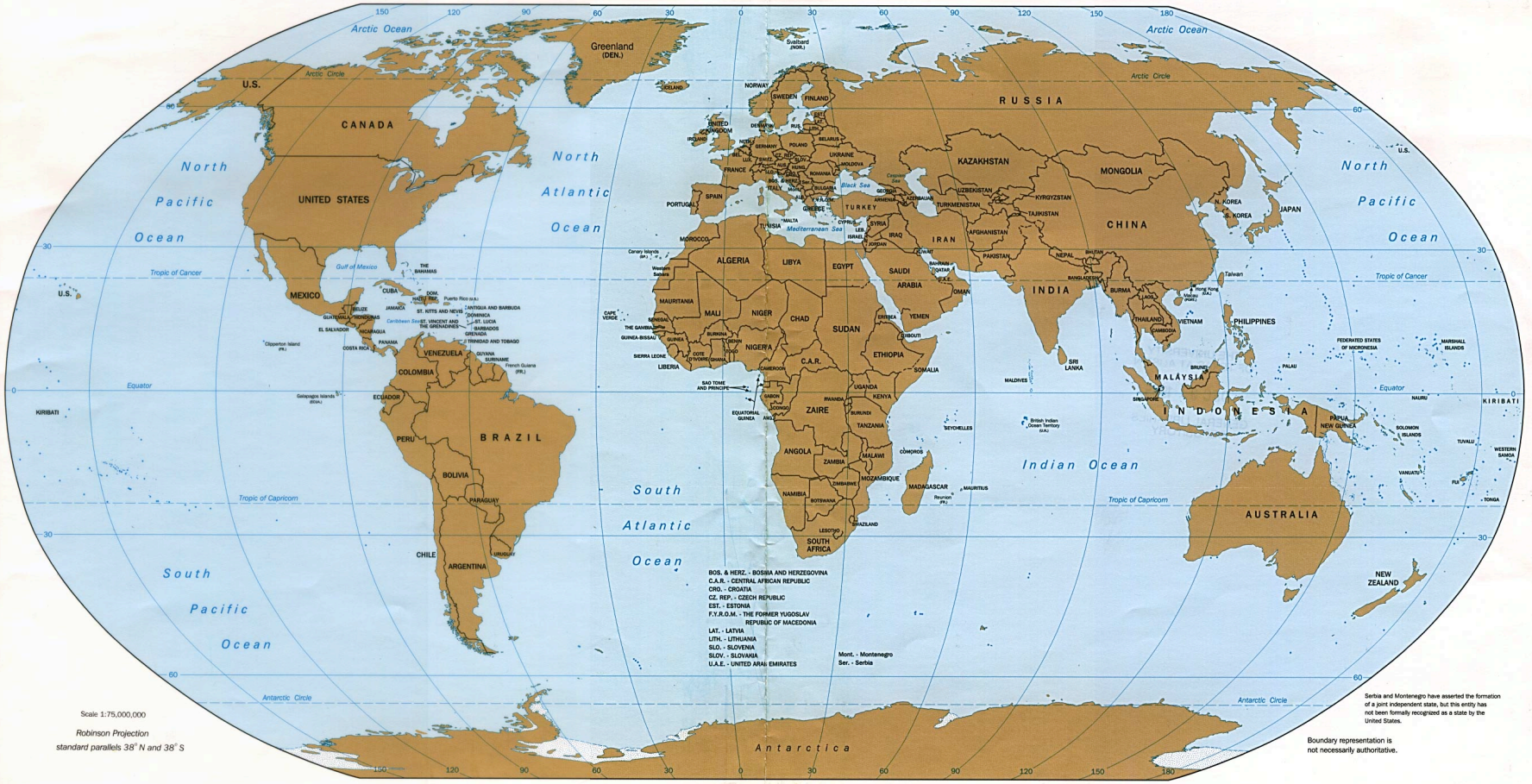
Position	Transcript	Transcript HGVS	Protein	Protein HGVS	Zyg	Effect
50824117	NM_001142933.1	c.19G>A	NP_001136405	p.Asp7Asn	het	non-synon
50824619	NM_001142933.1	c.112G>A	NP_001136405	p.Ala38Thr	het	non-synon
50856652	NM_020549	c.1382G>A	NP_065574	p.Val461Met	hom	non-synon
50863147	NM_020549	c.1642T>C	NP_065574	p.His548His	hom	synonymous

Pharmacogenetics

- MA is homozygous for a p.Ile359Leu change in CYP2C9, and this variant has been linked to a reduction in the enzymatic activity of CYP2C9, a member of the cytochrome P450 superfamily of enzymes.
- Cytochrome P450 proteins are mono-oxygenases, which catalyze many reactions associated with drug metabolism as well as reactions associated with the synthesis of cholesterol, steroids and other lipids.
- Fluoxetine is commonly used in the treatment of OCD; it has been shown to be as effective as clomipramine and causes less side effects.
- CYP2C9 acts to convert fluoxetine to R-norfluoxetine, and so MA may not be able to adequately biotransform fluoxetine.
- It is notable that MA had no response to an 80 mg daily dose of fluoxetine.
- However, CYP2C9 does not play a rate-limiting role for other SSRIs or clomipramine


z
y
x

Political Map of the World



Scale 1:75,000,000

Robinson Projection
standard parallels 38° N and 38° S

Serbia and Montenegro have asserted the formation of a joint independent state, but this entity has not been formally recognized as a state by the United States.

Boundary representation is not necessarily authoritative.

802373 (R00350) 4-95

Utah, New York and Faroe Islands

Will results from my blood tests be forwarded to me?

It will not be possible to give participants results of the blood tests. Due to regulations under the Clinical Laboratory Improvement Amendments (CLIA), we are legally unable to return research results to participants. Results from the blood tests will **not** be placed in participants' electronic health record. Participants should discuss any health concerns with their doctor or other health care provider, who can arrange any necessary and appropriate tests.

http://www.research.va.gov/mvp/veterans.cfm
accessed March 6, 2013

"A **partnership** is an arrangement where parties agree to cooperate to advance their mutual interests."- *Wikipedia*

PeerJ

Dealing with the unexpected: consumer responses to direct-access *BRCA* mutation testing

Uta Francke[1,2], Cheri Dijamco[1], Amy K. Kiefer[1], Nicholas Eriksson[1], Bianca Moiseff[1], Joyce Y. Tung[1], and Joanna L. Mountain[1]

[1] 23andMe, Inc., Mountain View, CA, USA
[2] Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA

204 *BRCA1* (185delAG or 5382insC) or *BRCA2* 6174delT mutation carriers (130 males and 74 females) in the 23andMe database of 114,627 customers who were at least 18 years of age and had consented to participate in research.

Clinical Validity with "Worldwide Human Genetic Variation Database" and/or "Medical Donor Information Network"?

ancestry.com

PatientsLikeMe

Google

23andMe

Million Veteran Program:
A Partnership with Veterans

100,000 British Genomes

The Empowered Genome Cohort

- **Gives PGP/UYG sequencees full access to secure platform for exploring and *sharing* genomes,** with each other *and with full-time researchers*, via Ingenuity Variant Analysis.

- **Helps citizen-scientists make their whole genomes at least modestly useful.**
  Today's q not what my genome can do for me, but *what our genomes can do for everyone.*

- **Leverages deep functional knowledge base & sensible comparison methods** (e.g., rare variant tests) to give current data silos (PGP/hard drives) a working bakery for collaborative insight.

- **Sequencees retain full control & rights to their private data.**

- **Upcoming talk @ ASHG (24 October, 9:15 Grand Ballroom East)**
  Teaser: Includes preliminary collaborative findings on myopia in 111 whole genomes…

- Contact Nathan Pearson (npearson@ingenuity.com) for details

Take Home Message

Genotype ≠ Phenotype

Environment matters!

Ancestry matters!

Genomic background matters!

Longitudinal course matters!

We can only begin to really understand this if we utilize the power of intense networking via internet-enabled archiving and distribution of consumer owned and managed data.

The End

Contents lists available at SciVerse ScienceDirect

Applied & Translational Genomics

journal homepage: www.elsevier.com/locate/atg

Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape

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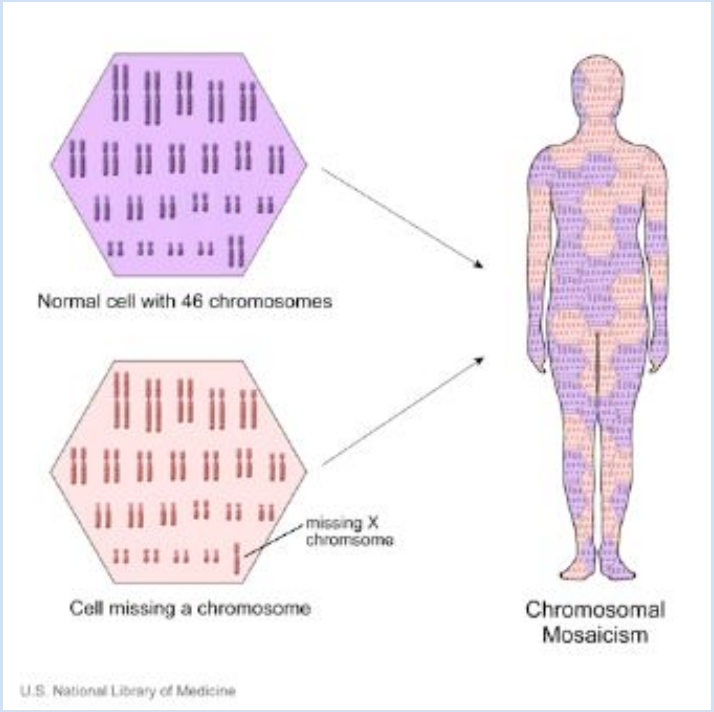
O'Rawe *et al. Genome Medicine* 2013, **5**:28
http://genomemedicine.com/content/5/3/28

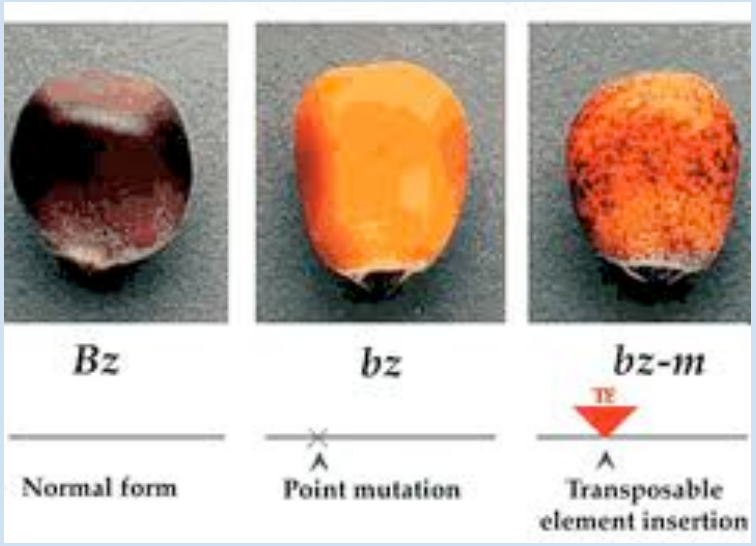
Genome Medicine

RESEARCH Open Access

Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing

Jason O'Rawe[1,2], Tao Jiang[3], Guangqing Sun[3], Yiyang Wu[1,2], Wei Wang[4], Jingchu Hu[3], Paul Bodily[5], Lifeng Tian[6], Hakon Hakonarson[6], W Evan Johnson[7], Zhi Wei[4], Kai Wang[8,9*] and Gholson J Lyon[1,2,9*]





Source: http://www.thenakedscientists.com/HTML/features/article/jamilcolumn1.htm/

OPEN ACCESS Freely available online

PLoS one

Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types

Julia Salzman[1☯], Charles Gawad[1,3☯], Peter Lincoln Wang[1], Norman Lacayo[3], Patrick O. Brown[1,2*]

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Abstract

Most human pre-mRNAs are spliced into linear molecules that retain the exon order defined by the genomic sequence. By deep sequencing of RNA from a variety of normal and malignant human cells, we found RNA transcripts from many human genes in which the exons were arranged in a non-canonical order. Statistical estimates and biochemical assays provided strong evidence that a substantial fraction of the spliced transcripts from hundreds of genes are circular RNAs. Our results suggest that a non-canonical mode of RNA splicing, resulting in a circular RNA isoform, is a general feature of the gene expression program in human cells.

Citation: Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO (2012) Circular RNAs Are the Predominant Transcript Isoform from Hundreds of Human Genes in Diverse Cell Types. PLoS ONE 7(2): e30733. doi:10.1371/journal.pone.0030733

Editor: Thomas Preiss, The John Curtin School of Medical Research, Australia

Received November 7, 2011; **Accepted** December 28, 2011; **Published** February 1, 2012